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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/341,196	07/06/1999	SUNITA DESOUSA	1103326-0571	4864

7470 7590 01/12/2004

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EXAMINER	
GABEL, GAILENE	
ART UNIT	**PAPER NUMBER**
1641	

DATE MAILED: 01/12/2004

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/341,196	DESOUSA ET AL.	
	Examiner	Art Unit	
	Gailene R. Gabel	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 September 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2-9* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2-9* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *20* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Amendment Entry

1. Applicant's amendment and response filed 9/24/03 and 10/30/03, in Paper Nos. 18 and 21, respectively, are acknowledged and have been entered. Claims 2 and 4 have been amended. Claims 2-9 are pending and are under examination.

Rejections Withdrawn

Claim Rejections - 35 USC § 112

2. In light of Applicant's amendment and argument, the rejection of claims 2-9 under 35 U.S.C. 112, second paragraph, is hereby, withdrawn.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was

not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

3. Claims 2, 4-5, and 8-9 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Mengin-Lecreulx et al. (Journal of Bacteriology, August 1991) in view of Elhammer et al. (WO 96/15258), and further in view of Shinabarger et al. (US 6,428,971) for reason of record.

Mengin-Lecreulx et al. teach that Escherichia coli murG gene codes for the UDP-N-Acetylglucosamine:N-Acetylmuramyl-Pentapeptide Pyrophosphoryl-Undecaprenol N-Acetylglucosamine transferase involved in the membrane steps of peptidoglycan synthesis. Specifically, Mengin-Lecreulx et al. analyzed activity of peptidoglycan precursors and determined the levels of translocase and transferase activities in membranes using crude extracts from strains of E. coli (see page 4628, column 1, and 4633). In cell fractionation experiments, Mengin-Lecreulx found that transferase is essentially associated with membranes and that inhibition of peptidoglycan synthesis occurs after the formation of cytoplasmic precursors (see Abstract).

Mengin-Lecreulx et al. is silent in teaching divalent metal ions, transglycosylase, and transpeptidase incorporated into a reaction mixture for experiments involving the membrane steps of peptidoglycan synthesis. However, divalent metal ions, transglycosylase, and transpeptidase inherently exist interactively and cooperatively as building blocks necessary for the formation of bacterial cellular membrane, i.e. required for the synthesis of peptidoglycan and therefore, are necessary structures and elements

so as to enable peptidoglycan formation and detection. Consequently, absence of detection which reflects lack or inhibition of biosynthetic activity in the reaction mixture is effected by lack/inhibition of these required elements necessary for the peptidoglycan synthesis.

Mengin-Lecreulx et al. differ from the instant invention in failing to disclose adding divalent metal ion chelator to the reaction mixture to terminate peptidoglycan synthesis.

Elhammer et al. disclose a Scintillation Proximity Assay for detection of reaction products wherein reaction mixture containing cellular membrane preparations with radiolabelled UDP-N-GalNAc and an intact acceptor protein or synthetic peptide are reacted and a divalent metal ion chelator such as EDTA is added into the reaction mixture to quench further reaction (see page 3, lines 18-30 and Examples 1 and 2 in pages 14 and 15). Elhammer et al. further disclose adding lectin-coated scintillation proximity beads into the reaction mixture wherein enzymatic transfer measurement is effected by measuring energy emitted by the radioactivity label (see page 4, lines 10-17 and page 8, line 30 to page 9, line 7). Elhammer et al. disclose that N - acetylgalactosamine (Gal-NAc) transferase enzyme is a cellular membrane enzyme that catalyzes the reaction that transfers Gal-Nac from the nucleotide sugar, UDP- N-acetylgalactosamine ((uridine 5-diphosphate) UDP-N-GalNAc) to amino acid residues on the acceptor polypeptide (see page 2, lines 10-16).

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to incorporate the teaching of Elhammer in adding divalent metal ion

chelator to the reaction mixture taught by Mengin-Lecreulx because Mengin-Lecreulx specifically studied and analyzed the activity of precursors and relevant enzymes in the membrane formation steps of peptidoglycan synthesis in E. coli and Elhammer specifically taught that divalent metal ion chelators such as EDTA can be added to cellular membrane preparations, such as those taught by Mengin-Lecreulx, having precursors and relevant enzymes undergoing reactions to terminate their reactions, if needed or desired.

Mengin-Lecreulx et al. and Elhammer et al. differ from the instant invention in failing to disclose that the beads bind specifically the radiolabelled sugar molecule, UDP-N-acetyl glucosamine in the synthesized peptidoglycan.

Shinabarger et al. disclose a Scintillation Proximity Assay wherein lectins such as wheatgerm agglutinin are bound to SPA beads to bind radiolabelled sugar molecules such as N-acetylglucosamine, in lipoteichoic acids isolated from a variety of gram positive bacteria. Shinabarger et al. specifically disclose that teichoic acid assists in maintaining the structural integrity of cell walls in bacteria, i.e. Staphylococcus, due to covalent attachment of peptidoglycan (see column 8, lines 46-52).

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to incorporate the teaching of Shinabarger in using SPA bead-bound wheatgerm agglutinin to bind N-acetylglucosamine for detection of peptidoglycan synthesis in the method of Mengin-Lecreulx as modified by Elhammer because Shinabarger specifically taught that application of wheatgerm agglutinin for immobilization to SPA as used by both Shinabarger and Elhammer, provides for specific

binding of scintillation proximity assay beads to sugar molecules such as N-acetylglucosamine, which is a precursor in the formation of peptidoglycan in methods of detecting peptidoglycan synthesis in bacteria as taught by Mengin-Lecreulx.

4. Claims 3, 6, and 7 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Mengin-Lecreulx et al. (Journal of Bacteriology, August 1991) in view of Elhammer et al. (WO 96/15258), and further in view of Shinabarger et al. (US 6,428,971) as applied to claims 2, 4-5, and 8-9 above, and further in view of Kohlrausch et al. (Journal of Bacteriology, June 1991) for reason of record.

Mengin-Lecreulx et al., Shinabarger et al., and Elhammer et al. have been discussed supra. Mengin-Lecreulx et al., Shinabarger et al., and Elhammer et al. differ from the instant invention in failing to disclose that the UDP-N-acetylmuramylpentapeptide is UDP-MurNAc-L-alanine-y-D-glutamic acid-m-diaminopimelic acid-D-alanine-D-alanine. Mengin-Lecreulx et al., Shinabarger et al., and Elhammer et al. further differ from the instant invention in failing to disclose including or adding to the reaction mixture a test compound which is an antagonist of the enzymes.

Kohlrausch et al. teach that peptidoglycan synthesis (formation of bacterial cell walls) occurs by prefabrication of soluble activated precursors: UDP-N-acetylglucosamine, UDP-N-acetylmuramyl-L-alanyl-D-glutamyl-m-diaminopimelyl-D-alanyl-D-alanine (UDP-MurNAc-pentapeptide) in the cytoplasm of bacterial cells such as E. coli. These are then translocated onto a lipid carrier, undecaprenyl-phosphate in

the cytoplasmic membrane (see page 3425, column 1 and page 3428, column 1). Kohlrausch et al. also teach that certain test compounds such as penicillin, D-cycloserine, and Moenomycin, act as antagonists to murein synthesizing enzymes which consequently lyse the cell wall structure (see Abstract and pages 3425, 3426, and 3428).

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to incorporate the teaching of Kohlrausch in testing the effects of test compounds, such as antagonists to enzymes that take part in peptidoglycan synthesis involving UDP-N-acetylmuramyl-L-alanyl-D-glutamyl-m-diaminopimelyl-D-alanyl-D-alanine (UDP-MurNAc-pentapeptide) as precursor, into the method of Mengin-Lecreulx as modified by both of Elhammer and Shinabarger because Kohlrausch specifically analyzed and taught the effects of enzyme antagonists in antibiotic-induced lysis of E. coli so as to provide guidance and allow assessment of antibiotic activity in other pathogenic bacteria involving cell membrane integrity, especially during peptidoglycan synthesis.

Response to Arguments

5. Applicant's arguments filed 10/24/03 have been fully considered but they are not persuasive.

A) Applicant argues that Mengin-Lecreulx differs from the instant invention in teaching use of paper chromatography to analyze reaction mixtures, as opposed to using divalent metal ion chelator compound to terminate peptidoglycan synthesis as

recited in step 2, and solution-phase detection of peptidoglycan biosynthesis, as recited in steps 3 and 4 of claim 2.

In response, claim 2 uses "comprising" language in the assay for detecting peptidoglycan synthesis; thus, does not exclude use of paper chromatography in subsequently analyzing for the presence of peptidoglycan in peptidoglycan biosynthesis.

B) Applicant argues that step 2) to terminate peptidoglycan synthesis and steps 3) and 4) for solution-phase detection of peptidoglycan synthesis, are neither taught nor suggested by Mengin-Lecreulx.

In response to applicant's arguments against Mengin-Lecreulx individually, wherein Mengin-Lecreulx fails to teach termination of peptidoglycan synthesis using divalent metal ion chelator in step 2) and solution-phase detection of peptidoglycan synthesis in steps 3) and 4), one cannot show nonobviousness by attacking references individually where the rejection is based on combination of the reference with Elhammer et al. and Shinabarger . See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). In this case, Elhammer is incorporated with the teaching of Mengin-Lecreulx for the use of divalent metal ion chelator such as EDTA added into reaction mixture containing enzymes to terminate reaction in Scintillation Proximity Assays (SPA) for detection of enzyme reaction products, as recited in step 2) of claim 2. Shinabarger is further incorporated for the teaching of a SPA using lectins such as wheatgerm agglutinin bound to beads to

bind radiolabelled N-acetylglucosamine as the sugar molecule in lipoteichoic acids in gram positive bacteria which assist in maintaining the structural integrity of cell walls due to covalent attachment of peptidoglycan. Accordingly, it would have been obvious to one of ordinary skill in the art at the time of the instant invention to incorporate the teaching of Shinabarger in using SPA bead-bound wheatgerm agglutinin to bind N-acetylglucosamine for detection of peptidoglycan synthesis in the method of Mengin-Lecreulx as modified by Elhammer because Shinabarger specifically taught that application of wheatgerm agglutinin for immobilization to SPA as used by both Shinabarger and Elhammer, provides for specific binding of scintillation proximity assay beads to sugar molecules such as N-acetylglucosamine, which is a precursor in the formation of peptidoglycan in methods of detecting peptidoglycan synthesis in bacteria as taught by Mengin-Lecreulx.

C) Applicant argues that there is no motivation to combine the teaching of Elhammer with that of Mengin-Lecreulx since Elhammer's SPA assay relates to eukaryotic (membrane bound) enzymes.

In response, Elhammer is incorporated with the teaching of Mengin-Lecreulx only for the teaching of divalent metal ion chelator such as EDTA used for addition into reaction mixtures containing enzymes in order to terminate reaction in SPA assays for detection of enzyme reaction products, as recited in step 2) of claim 2. The examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some

teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992).

D) Applicant argues that there is no motivation to combine the teaching of Shinabarger with that of Mengin-Lecreulx and Elhammer since Shinabarger relates to a different enzyme that is involved in cell wall teichoic acid pathway and is not involved in peptidoglycan synthesis.

In response, Shinabarger is incorporated with the teaching of Mengin-Lecreulx and Elhammer, only for the disclosure of wheatgerm agglutinin, i.e. lectin, used in SPA which is bound to SPA beads for binding to radiolabelled UDP-N-acetylglucosamine as sugar molecules in gram positive bacteria, to quantify the activity of enzyme. Accordingly, it would have been obvious to one of ordinary skill in the art at the time of the instant invention to incorporate the teaching of Shinabarger in using SPA bead-bound wheatgerm agglutinin to bind N-acetylglucosamine for detection of peptidoglycan synthesis in the method of Mengin-Lecreulx as modified by Elhammer because Shinabarger specifically taught that application of wheatgerm agglutinin for immobilization to SPA as used by both Shinabarger and Elhammer, provides for specific binding of scintillation proximity assay beads to sugar molecules such as N-acetylglucosamine, which is a precursor in the formation of peptidoglycan such as taught by Mengin-Lecreulx.

E) Applicant reiterates the current exceeding difficulty of characterizing downstream membrane-associated enzymes, such as those in the present invention and that the prior art fails to provide a simple solution-phase assay for the detection of peptidoglycan synthesis.

Applicant's argument regarding difficulty to characterize enzymes, as it relates to the recited claims is not on point since the claims recite a method to detect peptidoglycan synthesis by 1) incubating a reaction mixture comprising the precursors and enzymes which are the building blocks to the formation of peptidoglycan, 2) adding divalent metal ion chelator to terminate peptidoglycan synthesis, and 3) adding lectin-coated beads, in order to 4) measure radiation energy emitted by radiolabelled reaction product, i.e. peptidoglycan, all of which appear to read on the combined teachings of Mengin-Lecreulx, Elhammer, and Shinabarger. Accordingly, the rejection of claims 2-9, as currently recited, has been maintained.

6. No claims are allowed.

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gailene R. Gabel whose telephone number is (703) 305-0807. The examiner can normally be reached on Monday, Tuesday, and Thursday, 5:30 AM to 2:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long V. Le can be reached on (703) 305-3399. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4556.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 305-0169.

Christopher L. Chin

Gailene R. Gabel
Patent Examiner
Art Unit 1641
January 5, 2004

CHRISTOPHER L. CHIN
PRIMARY EXAMINER
GROUP ~~1800~~ 1641